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PERSPECTIVE

Linking up at the BAR: Oligomerization and F-BAR protein function

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ABSTRACT
As cells grow, move, and divide, they must reorganize and rearrange their membranes and cytoskeleton. The F-BAR protein family links cellular membranes with actin cytoskeletal rearrangements in processes including endocytosis, cytokinesis, and cell motility. Here we review emerging information on mechanisms of F-BAR domain oligomerization and membrane binding, and how these activities are coordinated with additional domains to accomplish scaffolding and signaling functions.

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Introduction

Dynamic cellular processes like motility, endocytosis, and cytokinesis require cells to remodel their membranes in concert with cytoskeleton reorganizations.[1] The Bin/Amphiphysin/Rvs (BAR) domain family of proteins is a central player in these processes, acting to link the plasma membrane to the actin cytoskeleton. The BAR protein family is defined by its membrane-binding BAR domain that folds into a dimeric, tightly interwound 6-helix bundle with a curved, crescent-like shape.[2,3] Structural studies have determined these domains interact with membranes through the concave face of their crescent-shaped structures.[2,3] However, not all BAR domains are shaped the same; multiple structural varieties exist, including classical BAR domains whose membrane-binding face is highly curved (BAR, N-BARs),[2] inverse BAR domains whose membrane-binding face bows outward to form a convex curve (I-BARs),[4] and Fer/Cip4 homology (FCH) BAR domains that form an elongated, shallow curve (F-BARs).[3] In this review we will focus on the banana-shaped F-BAR family. F-BAR domains are accompanied by a variety of other domains in proteins, including SH3, μHD, tyrosine kinase, or GTPase activating domains (GAPs) (Fig. 1). Here we will discuss recent work on F-BAR proteins with an emphasis on integrating F-BAR domain activities like oligomerization with functions of their additional domains in pursuit of a complete understanding of F-BAR protein function *in vivo*.

F-BAR domain activities

Membrane binding

The crescent-shaped F-BAR domain binds directly to membranes, localizing F-BAR proteins to various sites of action in cells. Emphasizing this important characteristic, membrane binding activity is essential for F-BAR protein function in all cases tested. For instance, point mutations within the FCHo2 and FBP17 F-BARs that specifically disrupt membrane binding prevent the proteins from localizing to the plasma membrane and sites of endocytosis.[5-7] Likewise, *Schizosaccharomyces pombe* Cdc15 or Imp2 membrane binding mutants are not functional.[8,9] Proteins lacking the F-BAR domain entirely also fail to properly localize and function: srGAP2ΔF-BAR and PACSINΔF-BAR fail to localize to the plasma membrane,[10,11] while *Saccharomyces cerevisiae* Hof1ΔF-BAR and Syp1ΔF-BAR lose localization to the bud neck[12,13] and sites of endocytosis,[14] respectively.

F-BAR domains interact with negatively charged membranes primarily through the concave face of their crescent shaped dimers, utilizing multiple positively charged surface residues.[3,8,9,15] PACSIN F-BAR domains also contain a unique amphipathic "wedge-loop" that partially inserts into the bilayer[16]; mutations in this region consequently disrupt membrane binding. The concave orientation of membrane binding is conserved in all F-BARs, though a few variations have been proposed. Under certain conditions *in vitro*, the FBP17 F-BAR domain associates with membranes through a side face,[7] and the Drosophila Nwk F-BAR has also been observed in a side conformation on membranes.[17] It is not yet clear if these alternative orientations are important for function or if they occur *in vivo*; mutations that disrupt this conformation must be tested for functionality *in vivo* to confirm that a sideways orientation is utilized in cells.

Given that F-BAR domains use positively charged residues for membrane binding, it is not surprising that they are generally capable of binding membranes containing

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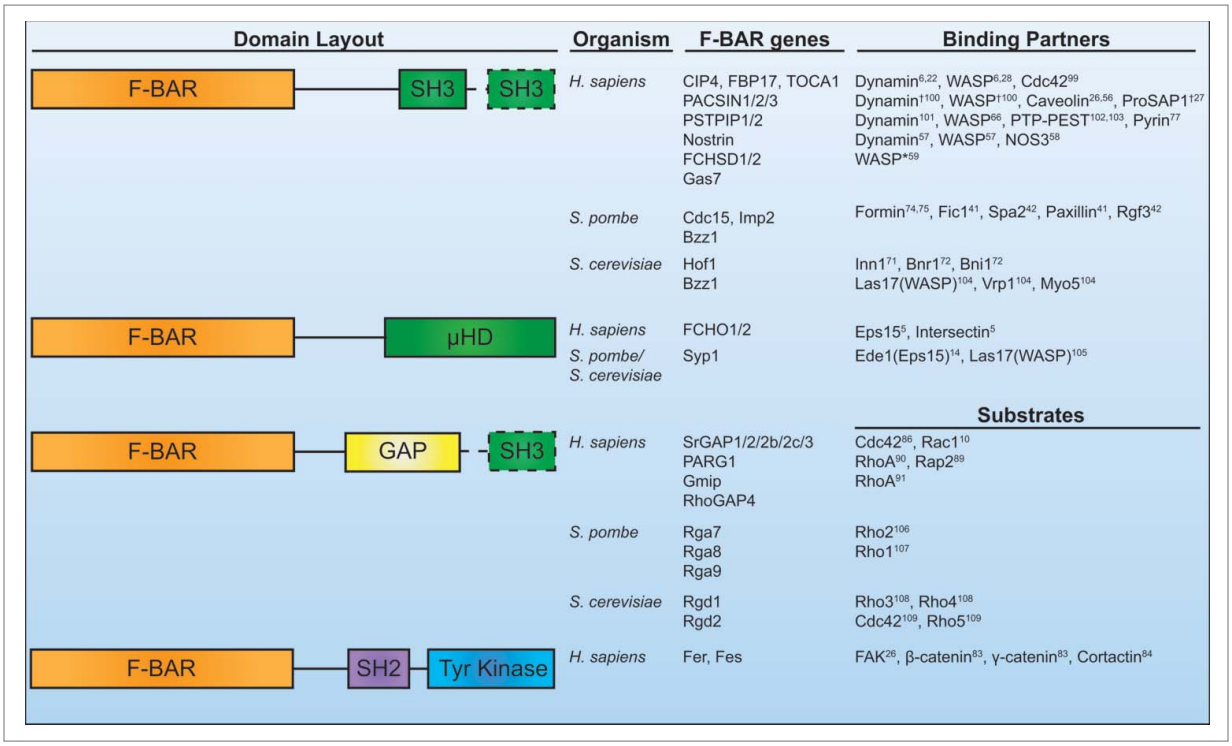

Figure 1. Human, *S. pombe*, and *S. cerevisiae* F-BAR proteins. Conserved domain layouts and select binding partners or substrates of human, *S. pombe*, and *S. cerevisiae* F-BAR proteins. Dashed lines indicate the domain is present only in a subset of the listed F-BAR proteins. *Indicates data from *Drosophila* homologs. †Indicates data from mouse or rat homologs.

negatively charged phospholipids. While most prefer phosphatidylserine (PS) or various phosphorylated phosphatidylinositol (PIP) lipid head groups, some F-BAR domains including srGAPs,[18,19] *Drosophila* Nwk,[17] and *S. pombe* Cdc15, bind membranes containing multiple species of PIPs.[9] Other F-BAR domains display a preference for a certain lipid, though this preference appears less stringent than that of other lipid binding domains such as pleckstrin homology (PH) domains.[20] FBP17 and CIP4 prefer PI(4,5)P_2 as well as PS,[6,21] PACSINs prefers PS,[21] Fer prefers phosphatidic acids,[22] *S. pombe* Imp2 prefers PI(4)P,[8] and *S. cerevisiae* Rgd1p prefers PI(4,5)P_2[15]. However, in all of these cases the F-BAR domains can bind membranes containing only PS as a negatively charged lipid *in vitro*.

In healthy eukaryotic cells, PS and PI(4,5)P_2 are exclusively located in the inner leaflet of the plasma membrane.[23] PS comprises ~2–10% of the inner leaflet of the PM, while PI(4)P and PI(4,5)P_2 are present in trace amounts (≤1 %).[23] Therefore preferences for PS and PI(4,5)P_2 may be important to direct F-BAR proteins to specific areas enriched in these phospholipids, like the plasma membrane or endocytic sites. Conversely, some evidence suggests this relationship works in the opposite direction; F-BAR proteins may serve to cluster certain plasma membrane lipids into stable micro-domains.[24] F-BAR domain-mediated clustering of lipids could be important for generating distinct lipid environments at cellular structures like endocytic sites,[25] caveolae,[26] or neuronal spines.[27] This hypothesis requires further investigation *in vivo*, perhaps with specific lipid sensors to assay for lipid organization defects in F-BAR membrane-binding mutants.

Oligomerization and membrane bending

Since the earliest characterizations of F-BARs, multiple F-BAR domains were observed not only to bind, but to bend membranes into thin tubules when present at high concentration.[6,21,28] Tubulation has been observed when certain F-BAR domains are added to liposomes *in vitro*, or when overproduced in cultured cells. F-BAR-coated membrane tubules formed in this manner adopt a range of diameters from ~50 to ~200 nm,[7,8] indicating a degree of flexibility in the F-BAR coat. This heterogeneity initially precluded structural determination of the F-BAR coat; however, Frost and colleagues generated homogenously coated tubules using careful *in vitro* slow-annealing methods. Using cryo-electron microscopy, the structure of the F-BAR coat upon these tubules was determined,[7] revealing that CIP4 F-BAR dimers oligomerize through complex lateral and tip to tip interactions to form a dense coat upon the membrane.[7,29] Accordingly, mutations that disrupt oligomerization of F-BAR domains prevent tubulation in overexpression assays.[7,8] Computational methods corroborate the oligomerization model of tubulation, as an assembly of oligomerized F-BAR domains can bend a flat membrane into a tubule in molecular dynamics simulations.[30] Attractive models proposing F-BAR domains oligomerize upon a membrane in order to collectively induce membrane curvature in endocytosis and other processes have arisen from these structural studies.[31-34]

Yet, the ability to induce inward-oriented membrane tubules isn't conserved in all F-BAR domains. srGAP F-BAR domains induce tubules of the opposite curvature, outward from the plasma membrane.[10,19] This curvature generation is likely

accomplished through similar mechanisms as I-BAR proteins, which also oligomerize to collectively bend a membrane.[35] Recent evidence suggests even these two varieties of membrane tubulation do not adequately describe the functions of all F-BAR family members. In fact, multiple F-BAR proteins do not tubulate membranes in standard *in vitro* liposome binding or cultured cell overexpression assays. These include: Fer,[6] Fes, RhoGAP4, Gas7, and FCHSD1/2,[9] as well as *S. pombe* Cdc15,[9] *S. cerevisiae* Hof1,[15] and *Drosophila* Nwk.[17]

It could be argued that the perfect condition (such as a specific lipid composition) has not been discovered to support tubulation of these F-BARs. However, cultured cells contain a variety of membranes with different compositions that overexpressed F-BAR domains can access,[36] so this seems an unlikely possibility. Also, multiple compositions mimicking physiological membranes have been tested *in vitro*, as well as lipid extracts from tissue.[9] Synthetic membrane conditions with higher concentrations of PIPs or other lipids depart from a realistic cell-like environment. Further, sufficiently concentrating any protein upon a membrane by adding more binding sites (such as PIPs) is sufficient to induce tubulation through molecular crowding effects.[37] A simple explanation for the observed lack of tubulation is certain F-BAR domains do not oligomerize in a manner that confers tubulation activity. And indeed, despite not tubulating membranes, these F-BAR domains do oligomerize.[9,17,38-40] Membrane tubulation by F-BAR domains, therefore, appears be one specific consequence of a generally shared ability to oligomerize and simultaneously bind membranes.

One example of an oligomerization mechanism that does not lead to membrane tubulation can be found within the *S. pombe* Cdc15 F-BAR. EM studies showed this F-BAR domain oligomerizes into linear filaments even in the absence of membrane[9] through direct tip to tip electrostatic interactions between F-BAR dimers. Other examples include oligomerization of the *Drosophila* Nwk F-BAR, which forms short zig-zag structures that can subtly bend and pucker membranes *in vitro*,[17] and lateral contacts between dimers of the Fer and RhoGAP4 F-BAR domains.[9] Each case of F-BAR oligomerization studied so far has defined a distinct mechanism of dimer-dimer interaction; F-BAR domains therefore have evolved multiple ways to link together. Further investigation will be necessary to determine the full complement of oligomerization mechanisms used by this protein domain. Targeted mutagenesis of prominent charged surface patches on the tips and sides of F-BAR domains (which could mediate dimer-dimer interactions), and subsequent screening for loss of oligomerization has previously been successful in identifying oligomerization interfaces.[9]

Oligomerization that does not lead to tubulation nevertheless appears central to F-BAR protein function. Cdc15's linear oligomerization supports a robust avidity (as each repeating F-BAR unit has membrane binding contacts) toward a flat membrane surface. This high avidity membrane binding is critical to accumulate and stabilize Cdc15 at the cell division site[9] where it recruits and scaffolds multiple cytokinesis proteins.[41,42] Mutations that disrupt F-BAR oligomerization sharply decrease the abundance and increase the turnover of Cdc15 at the division site, which consequently leads to cytokinetic failures.[9] Mutations in Fer that block oligomerization compromised its ability to induce lamellipodia formation and enhance cell migration, possibly due to a loss of strong localization to the leading edge membrane.[9] Additionally, mutations in the RhoGAP4 F-BAR that disrupt oligomerization compromised RhoGAP4's ability to inhibit cell migration.[9] These examples highlight what may be a generally important characteristic of F-BAR domains - their ability to form oligomers on membrane surfaces for the purpose of scaffolding additional protein elements or forming signaling centers.

Surprisingly, the importance of oligomerization for physiological function in the cases of tubulating F-BARs has rarely been directly tested, though it is clear that blocking oligomerization inhibits tubulation of liposomes *in vitro* and of the plasma membrane in mammalian cell overexpression assays.[7] In other words, whether the tubulation activity of F-BAR proteins *in vitro* is connected to their functions *in vivo* has not been rigorously established in most cases. To our knowledge, this connection has been tested in only two cases of tubulating F-BARs and different results have been obtained. In the first, it was found that patient derived mutations in FCHO2 that block oligomerization but not membrane binding inhibit FCHO2 recruitment to endocytic sites.[5] This may be due to a reduction in membrane binding avidity, similar to the case of Cdc15. In the second, mutations that block oligomerization and tubulation of *S. pombe* Imp2 have no discernable impact on its localization or function.[8] While this is still surprising, the lack of oligomerization may be compensated for by other protein-protein interactions which enforce a local concentration of Imp2 at the division site.[42] Clearly though, these examples highlight the value of clarifying the importance of F-BAR domain oligomerization in other F-BAR proteins. As it is now established that F-BAR domains utilize different interaction surfaces to bind one another and oligomerize, this will not be a simple matter of creating homologous mutations, but will require elucidation of each protein's mechanism of oligomerization.

Considering the diversity of oligomerization modes and their functional importance, we propose F-BAR domains in general act as membrane binding, oligomerizing modules that serve to concentrate and stabilize F-BAR proteins at sites of action (Fig. 2). Beyond this generalization, it is likely that different F-BAR domains possess oligomerization interactions that are tailored for distinct functional contexts. When F-BARs are organized by cellular functions, some trends emerge: many endocytic F-BAR domains possess oligomerization interactions that confer binding to or may induce curved membranes (such as FBP17, CIP4, and PACSINs), while F-BARs involved in cytokinesis or cell migration are tuned to bind a relatively "flat" plasma membrane (including Fer, Fes, RhoGAP4, and *S. pombe* Cdc15) (Fig. 2).

Additional domains

F-BAR domain membrane binding and oligomerization are only part of an F-BAR protein's job. Once an F-BAR is bound and oligomerized upon a membrane, it utilizes additional domains to perform scaffolding and signaling functions.

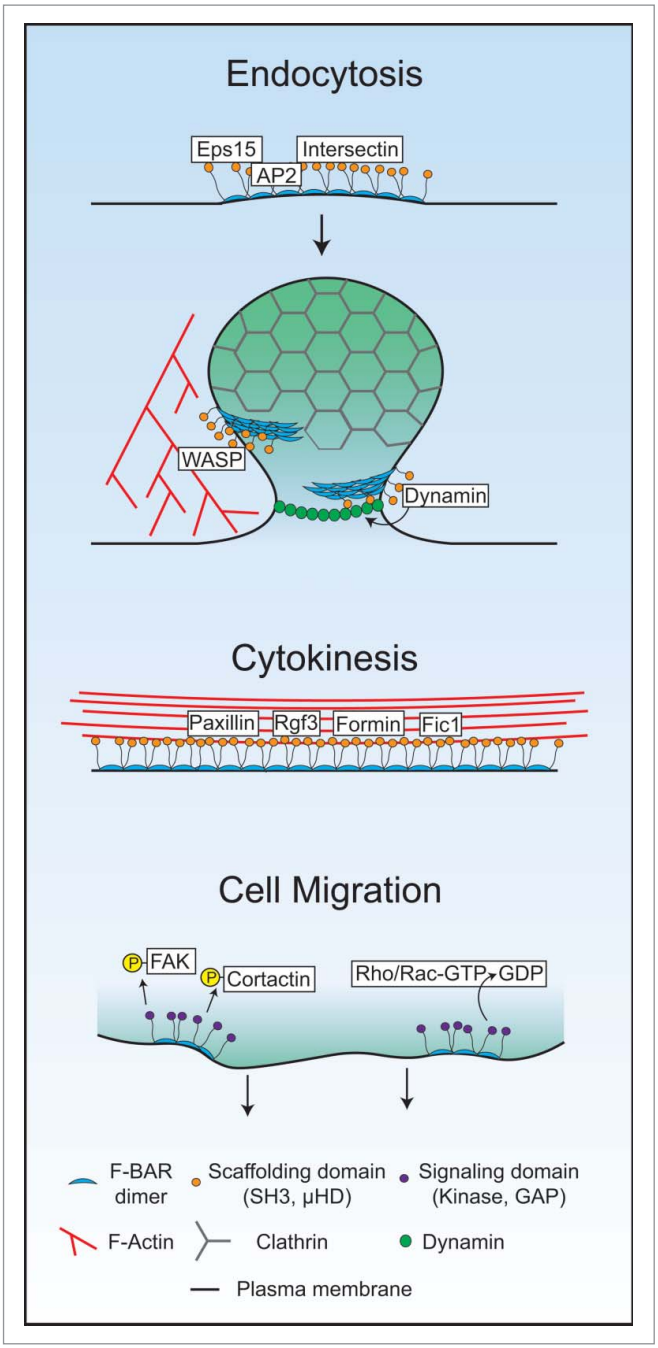

Figure 2. Diverse modes of F-BAR oligomerization in endocytosis, cytokinesis, and cell migration. Schematics of possible modes of F-BAR protein oligomerization, protein recruitment, and signaling in endocytosis, cytokinesis, and cell migration.

Scaffolding functions

The majority of F-BAR proteins contain either a SH3 or μHD domain that they use to connect with other proteins (Fig. 1). In the cases of F-BAR proteins involved in endocytosis, they recruit partners that in turn have scaffolding and protein recruitment functions. For example, FCHO1/2 F-BAR proteins are two of the first components to localize at incipient sites of endocytosis.[5] FCHO2 uses a μHD domain to directly recruit Eps15 and Intersectin,[5] and an unstructured middle region to bind and allosterically activate AP2.[43,44] In yeast, Syp1 acts similarly; it is present early at sites of endocytosis and recruits Ede1, an Eps15 homolog.[14,45]

The tubulating activity of FCHO1/2 F-BAR domains[3] led to the idea that they might induce the initial membrane curvature early at an endocytic site.[5] However, single-molecule imaging experiments suggest that FCHO1/2 "stabilize" the growing bud but do not initiate curvature.[46] Efficient recruitment of binding partners and activation of AP2,[43,44] aided by clustering from oligomerization,[5] may instead explain how FCHO2 acts as a nucleator of clathrin-mediated endocytosis. Indeed, multiple other proteins at endocytic sites are likely responsible for curvature generation, including the FCHO2 binding partner Eps15,[47,48] multiple classical BAR domain proteins,[33] and the triskelion clathrin coat.[49]

Slightly later in endocytosis, FBP17 and CIP4 F-BAR proteins bind the budding vesicle.[50] FBP17 and CIP4 may contribute to branched actin network formation at the endocytic site through SH3 domain-mediated recruitment of Arp2/3 activators WASP[6,51,52] and, for CIP4, WAVE.[53] Both FBP17 and CIP4's SH3 domains also recruit the GTPase Dynamin,[6,21,28,50] a critical component for vesicle scission[54] (Fig. 2). The PACSIN group of F-BAR proteins similarly scaffold WASP and Dynamin and are present in clathrin-mediated endocytosis in certain cells,[55] as well as caveolar endocytic sites.[26,56] Nostrin also functions at caveolae by recruiting WASP, Dynamin, and a specific substrate, nitric oxide synthase, to regulate its internalization.[57,58] *Drosophila* Nwk proteins correspondingly recruit WASP,[59] Dynamin,[60] and sorting nexin Snx16[61] in neurons to regulate synaptic growth receptor signaling at presynaptic neuromuscular junctions.[61,62] Therefore, multiple F-BAR proteins at endocytic sites in different cell types build branched actin networks through recruitment of WASP or WAVE, and assist in vesicle scission through recruitment of Dynamin.

In other cellular processes, F-BAR proteins perform similar scaffolding functions to bridge the membrane to the actin cytoskeleton. As examples, CIP4's binding and recruitment of WASP is also important in regulating lamellipodia during cell migration,[63,64] and seems to be a critical component inducing invadopodia in cancer cells.[65] In neurons, PACSIN2 interacts with ProSAP1 to form stable membrane-bound structures in neural spines (presumably through oligomerization) which regulate spine organization.[27] Furthermore, the PSTPIP1 F-BAR protein scaffolds PTP-PEST phosphatases together with substrates such as WASP[66,67] and Abl[68] to modulate the actin cytoskeleton.

Model organism studies have also contributed to our understanding of scaffolding F-BAR proteins. In fission yeast, the Cdc15 and Imp2 F-BAR proteins are membrane-bound components of the contractile ring.[69,70] Using redundant SH3 domains, these proteins recruit crucial contractile ring proteins including Fic1, Spa2, Rgf3, and Pxl1.[41,42] Oligomerization by Cdc15 is critical to localize its partners; oligomerization mutants recruit ~50% less SH3 binding partners, compromising cytokinesis.[9] In *S. cerevisiae*, the homologous Hof1 F-BAR protein is also important for cytokinesis, recruiting Inn1 through its SH3 domain which activates the chitin synthase necessary for division.[71] Hof1's SH3 domain also binds the cytokinetic formin Bnr1,[72] which "tunes" the formin's activities.[73]

While many F-BAR proteins use μHD and SH3 domains for scaffolding functions, in certain cases F-BAR domains also interact directly with other proteins. For example, the *S. pombe* Cdc15 F-BAR domain directly binds and recruits the formin Cdc12,[74,75] which is responsible for F-actin formation in the contractile ring.[76] Human PSTPIP1's F-BAR domain interacts with Pyrin[77]; this interaction activates Pyrin to initiate pyroptosome formation and an inflammatory response.[78] It is possible that these two interactions occur simultaneously with membrane binding; the F-BAR domain could bind the membrane on its concave face and a partner on its opposite, cytoplasmic face. In contrast, the PACSIN2 F-BAR domain can interact directly with F-actin filaments *in vitro* through its concave face[79]; this interaction excludes simultaneous membrane binding. The cytoplasmic face of F-BAR domains may represent a more generally utilized surface for F-BAR proteins to form linkages with other proteins upon the membrane than currently appreciated.

Based upon much work in the field since their original description, it is clear that many F-BAR family proteins serve as membrane bound scaffolds for a variety of binding partners (Fig. 1). Oligomerization through their F-BAR domains aids scaffolding by locally concentrating the proteins upon membranes. SH3 domains have relatively low affinity (~1–100 μM) for substrates[80]; F-BAR oligomerization may therefore help to build a high density network of SH3 or μHDs to strongly link with actin cytoskeletal partners (Fig. 2).

Signaling functions

Other F-BAR proteins contain protein kinase or GAP domains (Fig. 1) and act as signal transducers to the cytoskeleton. Fer and Fes are unique non-receptor tyrosine kinases whose F-BAR domains localize the proteins to the leading edges of migrating cells[22] or focal adhesions,[81] respectively. Fer and Fes F-BAR domain oligomerization impacts activation of their tyrosine kinase domains through trans-phosphorylation,[38,39] similar conceptually to how receptor tyrosine kinase clustering promotes trans-activation. When activated, Fer and Fes phosphorylate several substrates including FAK,[82] β- and γ-catenin,[83] and cortactin[84] to modulate cell-cell and cell-matrix contacts.[85]

The last class of F-BAR proteins contain GTPase activating domains (GAPs) that promote GTP to GDP catalysis by small GTPases. The most well studied of these in humans is the srGAP group. srGAP1/2/2b-c/3 participate in neural morphogenesis and migration.[18,86] srGAP1 is a critical effector of repulsive Slit-Robo signaling; ROBO1 bound to extracellular SLIT2 activates srGAP1s GAP domain at the membrane to specifically inactivate the Cdc42 GTPase, leading to actin cytoskeletal changes that decrease migration toward the SLIT2-displaying cells.[86] srGAP2 is important for the biogenesis of neurites,[10,87] as well as regulation of Slit-Robo mediated contact inhibition during cell migration through its GAP domain's inactivation of Rac1.[88] Additional F-BAR GAP proteins in humans include PARG1, Gmip, and RhoGAP4. PARG1 and Gmip's GAP domains target RhoA,[89-91] while RhoGAP4's substrates are unknown. RhoGAP4 functions in inhibiting cell migration,[92] but little is known about PARG1 and Gmip cellular function.

Significant future study is required to understand the substrates of signaling F-BARs and integrate this functionally with their F-BAR domain activities.

Future directions

We have discussed the various activities of F-BAR domains (membrane binding, oligomerization, partner binding, signaling); however, these activities are not constitutive in cells, but instead are dynamically regulated. In fact, the membrane and partner binding capacity of many F-BAR domain proteins are autoinhibited and specific activation is required to allow these proteins to carry out their functions (reviewed in Roberts-Galbraith and Gould[93]). Phosphoregulation is one mechanism that allows for dynamic regulation in line with the short time windows of F-BAR protein activity in dynamic processes. Detailed analyses of phosphoregulation have been carried out for only a few F-BAR proteins such as *S. pombe* Cdc15[40,94] and *S. cerevisiae* Hof1,[12,95] and thus there is the opportunity to learn more about how F-BAR protein function is integrated in signaling networks, particularly in human cells. In other cases, it is argued that a binding partner pries apart an intramolecular interaction to release the F-BAR domain for membrane binding.[96,97] Further investigation is necessary to identify the molecular mechanisms of human F-BAR protein spatial and temporal activation.

In certain processes we have described such as endocytosis and cell motility, multiple F-BAR proteins participate simultaneously. In these cases, it is not clear to what extent F-BAR proteins have overlapping or distinct functions. It is possible that multiple F-BAR proteins, through different oligomerization, membrane binding, or partner binding properties, act together or sequentially to coordinate these processes. One approach that could begin to tease this complexity apart is F-BAR domain swapping experiments. These types of experiments will clarify the importance of specific functionalities within different F-BARs such as unique modes of oligomerization or selective membrane binding preferences, and determine whether there is plasticity between different F-BAR domains.[8] As discussed above, this will also require elucidation of each F-BAR domains' mechanism of oligomerization.

Finally, most studies of F-BAR proteins to date (and studies of proteins in cultured cells in general) rely upon exogenous expression and overexpression in cultured cells. With the advent of efficient genome editing methods such as CRISPR,[98] it is becoming simpler to study endogenous proteins and make mutations of genes at the endogenous locus in human cells. Endogenous mutations and fluorescent tags will refine our knowledge of F-BAR protein localization and functionality in different circumstances. Working in the absence of wildtype protein and with correct endogenous expression levels will further remove many confounding effects of exogenous expression studies, including artificial membrane tubulation by highly concentrated F-BAR proteins.

Abbreviations

BAR	Bin/Amphiphysin/Rvs domain
FCH	Fer/CIP4 homology
F-BAR	FCH-BAR domain
SH3	SRC homology 3 domain

μHD	muniscin homology domain
GAP	GTPase activating domain
FAK	focal adhesion kinase
PIP	phosphorylated phosphatidylinositol

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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